# Final Subcommittee Report

## Introduction

In response to the recognition of problems with comparisons of data on carcinoma in situ of the cervix uteri over time and across areas, AACCR's Uniform Data Standards Committee, through a planning subcommittee, convened a working group on pre-invasive cervical neoplasia and population-based cancer registries to provide a status report on the terminology, diagnostic criteria, and treatment in use today and in the future, and to formulate a set of recommendations for member registries. The Committee assembled a group of experts in pathology, obstetrics and gynecology, cancer control, viral etiologic research, epidemiology, and cancer registries. Abstracts of the presentations are included in this report, along with a list of the participants and the planning committee members.

## Narrative Summary

Most population-based cancer registries in the United States attempt to collect carcinoma in situ (CIS) of the cervix uteri, which comprises approximately 5-7% of the usual caseload. Most U.S. registries follow the lead of the National Cancer Institute's SEER program in determining their reportable list, and in 1984, SEER added CIN III (cervical intraepithelial neoplasia, grade III) as a reportable synonym for carcinoma in situ of the cervix uteri. Many other registries are also now collecting CIN III. CIN III is included in the International Classification of Diseases for Oncology, 2nd ed., (ICD-O-2) as an in situ neoplasm, with the code 8077/2.

The 3-tier CIN system is used by many histopathologists in place of the previous 4-tier system, which distinguished mild, moderate, and severe dysplasia, and CIS. The designation of CIN III actually includes both severe dysplasia and CIS, but SEER and ICD-O did not provide for inclusion of the term "severe dysplasia" without a CIN III designation as reportable. Many registries have adopted the SEER guidelines of registering cases diagnosed as CIS or CIN III, but not those termed "severe dysplasia" only. In areas where pathologists are still using the 4-tier terminology, unless registries also collect cases of severe dysplasia as well as CIN III, the comparability of data within and between registries will be difficult at best. (See abstract of Ries.)

The Bethesda System (TBS) terminology for cytopathology divides the continuum of pre-invasive-cancer changes into two tiers--low grade and high grade squamous intraepithelial lesions, LGSIL and HGSIL. HGSIL includes what was called in the 3-tier system CIN II and III, and what was called in the 4-tier system moderate dysplasia, severe dysplasia, and carcinoma in situ. LGSIL includes HPV (human papillomavirus) changes and what was termed mild dysplasia in the 4-tier system, or CIN-I in the 3-tier. (See fig. 1, page 5) TBS has been adopted by most cytopathology laboratories in the U.S. It is anticipated that TBS will be increasingly used for histopathology diagnoses as well, and that this increase will occur as laboratories find it more convenient to use one system of nomenclature rather than two, and as the proportion of pathologists who have been trained since the widespread adoption of TBS increases. There may also be some regulatory pressure to use TBS for histopathology, although at this time no national organization or regulatory group has recommended TBS for histopathology. (See abstracts of Solomon, Scully, Richart, and Wertlake.)

It is also likely that the adoption of TBS for histopathology will vary across the country. In some unknown proportion of diagnoses using TBS, the diagnosis may also be given in the 3- or 4-tier terminology (e.g., "HGSIL, CIN III"), but this will not always be the case. As the use of TBS becomes widespread, the proportion of cases with a diagnosis stated in both TBS and either the 3- or 4-tier system is expected to drop.

In the more distant future, the diagnoses may be made on the basis of molecular probes for HPV instead of the morphology/histology of the lesions.

Clinical management of CIN II, CIN III, moderate or severe dysplasia, CIS, or HGSIL, is generally similar. Patients with any of these diagnoses on cytology go on to colposcopic biopsy and LEEP (loop electrocautery excisional procedure) excisions, increasingly done in physicians' offices and surgery centers, or conizations most often done in hospitals. Other therapeutic procedures will be done less often for these lesions. Thus the histopathology specimen will often represent the treatment for this spectrum of conditions, and will represent a cancer control intervention.

The natural history of HPV infection and the spectrum of pre-invasive cervical lesions is not completely understood, and those involved in cancer etiology research involving HPV see as desirable some mechanism of registering all SIL, low and high grade, with long term follow-up of patients to determine outcomes. (See abstracts of Kurman and Sherman.) However, this is beyond the scope of the routine data collection efforts of cancer registries as presently constituted, and would better be accomplished through special study design and funding.

Although many registries are now collecting CIS (and often including CIN III, sometimes distinguishable from CIS and sometimes not), the data have not often been used. Incidence rates have rarely been published, and states' cancer-control programs have often not used the registry data on pre-invasive neoplasia for program planning or evaluation of interventions. (See abstracts of Haenlein and Qualters.) The AACCR cancer control project, part of a cooperative agreement with CDC, determined that stage-specific incidence rates of invasive cervical cancer were the appropriate registry-based measures for cancer control programs. (See abstract of Franks.)

In a geographic area where pathologists are known to use the same diagnostic criteria and terminology (see abstract of Friedell) or there are no biases in case ascertainment or diagnostic criteria across population subgroups, registry data on pre-invasive neoplasia may be used to compare population subgroups at a point in time to identify variations in screening activity. (See abstracts of McWhorter, Smith, and Young.) Unless uniformity in histopathology reporting is present, however, data cannot be compared over time or across areas, and in practice, biases may be inherent in the data and not easy to detect or evaluate.

Data that have been collected for the terms CIS plus CIN III are no longer comparable to earlier data for CIS alone. Obtaining data that are comparable over time requires collection of all HGSIL and its equivalent terms in the 3- and 4-tier systems, but these data would not be comparable to historic data for CIS or CIS plus CIN III, and would require significantly more resources to collect.

Separate from the problem of changing terminology and diagnostic criteria, there are other changes in medical practice that will make it increasingly difficult to obtain routine reporting of these cases. Diagnosis and treatment is becoming increasingly decentralized. In the future, most family practice residency programs will train residents in performing colposcopy and probably LEEP, and the cost of the equipment is low enough that many physicians will have the equipment in their offices. Cost containment efforts will influence the choice of pathology laboratories, and increasingly physicians may be sending specimens to out-of-state labs for processing. Since lab records often lack the demographic information needed to complete a cancer registry abstract, follow-back to the clinicians' records is often required. Routine registration of even the same number of cases will thus require added resources for both case ascertainment and abstracting, and any efforts to make registration more complete, by adding "severe dysplasia" and/or HGSIL, will add 2-3 times the number of cases to be registered, requiring even more resources.

In summation, there are longstanding problems of comparability of data on pre-invasive carcinoma of the cervix uteri which will only get worse. Solutions will require either dropping the collection of these data or expanding the collection of data to include all HGSIL and its equivalent terms. In the context of static or decreasing resources, the SEER program will likely discontinue the routine collection of CIS/CIN III in most geographic areas of the SEER program and institute instead an expanded coverage of all HGSIL in selected geographic areas which have ethnically and economically diverse populations. The areas which collect HGSIL will be provided with added resources. Specific codes are needed for each diagnostic term of interest, since ICD-O-2 provides codes for CIS and CIN III only. The issue of legal access to records of cases of CIN II or dysplasia by cancer registries will also have to be addressed.

# Conclusions and Recommendations

- Data on pre-invasive cervical neoplasia as currently collected by U.S. registries are no longer comparable historically for monitoring trends over time and cannot be made to be comparable. The problem will get worse as TBS is more widely adopted for histopathology. Collection of only the term “CIS” yields undercounts in recent data compared to the past. Collection of both of the terms “CIS” and “CIN III” yields overcounts in comparison to the past.

- In the future, it will not be possible in every case to distinguish moderate dysplasia, severe dysplasia, and CIS on pathology reports.

- There is evidence that the relative use of the 3-tier, 4-tier, and TBS systems varies from place to place within the U.S. Comparability of current data across registries is limited by different rates of differences in terminology used on pathology reports.

- Data as presently collected can be used to monitor differences in sub-populations within a geographic area as long as biases in diagnostic criteria and case ascertainment are not present. Pre-invasive rates help to interpret differences in invasive rates, and in situ/invasive ratios in particular appear to have implications for prevention activities.

- Adjacent "grades" of pre-invasive lesions are more difficult to distinguish one from another and less reproducible than the distinction between invasive and non-invasive lesions.

- Treatment is becoming more conservative and more uniform for HGSIL and the other equivalent terms. Since colposcopic biopsy and LEEP can be therapeutic as well as diagnostic, histologic diagnoses of pre-invasive lesions represent cancer control intervention. Fewer ablative procedures will be done without tissue diagnosis, so this is not expected to be a significant source of missed cases.

- As is true to some extent for other cancer sites, diagnosis and treatment are moving out of the hospital setting. It will become more and more difficult and expensive to find cases and collect required demographic data, such as the patient's race and place of residence. Out-of-area laboratories will likely be a problem and will be an increasingly important source of missed cases.

- SEER, which sets the de facto reporting standard in this area, will likely drop the routine collection of CIS and CIN III in all areas and instead expand collection to include HGSIL and its equivalent terms in selected areas, with special funds.

## Recommendations

1. The only way to collect histologic data which would be comparable over time in the future is to collect all HGSIL and all of its equivalent terms in the 3- and 4-tier systems. This would increase the number of pre-invasive cervix uteri cases in a registry which now collects CIS and CIN 3 by approximately 2 to 3 fold. The new data would not, however, be comparable to data collected earlier.

2. For research on the natural history of this disease, special studies which include the entire spectrum of LGSIL and HGSIL would be necessary.

3. Population-based registries need to assess locally the anticipated uses of the data (are time trends desirable? are comparisons to data from other areas needed? will cancer control programs use the data?), present and future pathology practices in their area (will TBS be used for histopathology?), and the available resources (can the registry afford to collect substantially more cases?), and decide whether to:

    - collect CIS, CIN III, and severe dysplasia, which will not be possible if TBS is used for histopathology,

    - collect all HGSIL and its equivalent terms in the 3- and 4-tier systems, which will substantially add to the caseload, or

    - drop collection of all data for all but invasive cervical cancers.

    The Subcommittee strongly recommends that population-based registries discontinue routine collection of data on pre-invasive cervical neoplasia unless there is strong local need and interest and sufficient resources are available to collect all HGSIL and its equivalent terms.

Figure 1: Simplified Comparison of Diagnostic Systems
For Pre-Invasive Cervical Neoplasia

| 4-tier | 3-tier | TBS |
|---|---|---|
| mild dysplasia | CIN I | LGSIL |
| moderate dysplasia | CIN II | HGSIL |
| marked or severe dysplasia | CIN III | |
| carcinoma in situ | | |